Fab Expression Vector pAK19
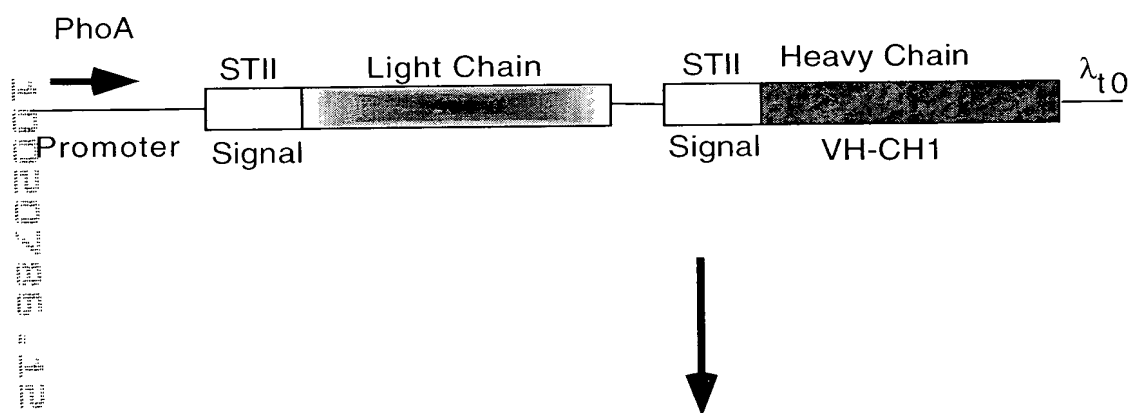
Full Length Antibody Expression Vector Derived from pAK19
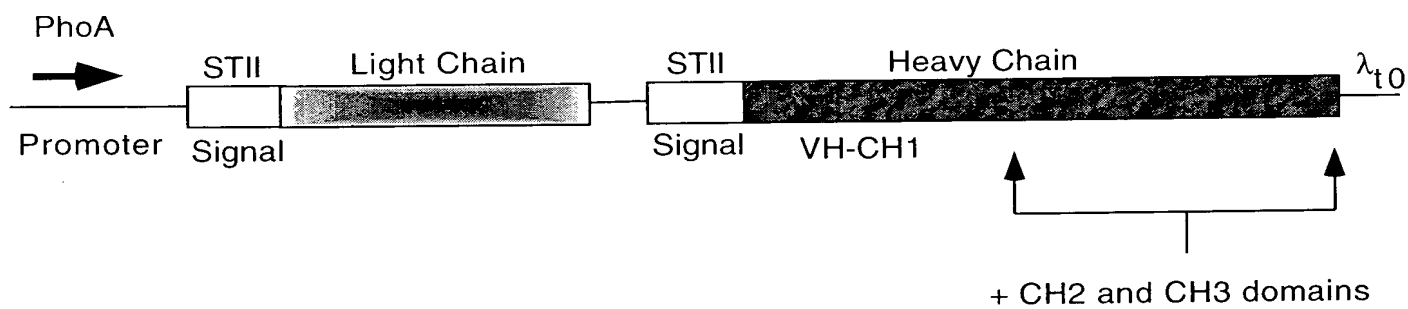
Figure 1

Figure 2

Polycistronic Constructs

	STII	light chain	STII	heavy chain	
	TIR		TIR		
	1		1	paTF20	
	3		1	paTF30	
	1		3	paTF40	
	3		3	paTF90	
	7		3	paTF110	
	3		7	paTF100	
	7		7	paTF120	

Figure 3.

polycistronic
reduced

neg.	1L 1H	3L 1H	1L 3H	3L 3H	7L 3H	3L 7H	7L 7H

4A

——— heavy

——— light

polycistronic
non-reduced

neg.	1L 1H	3L 1H	1L 3H	3L 3H	7L 3H	3L 7H	7L 7H

4B

foldedH
Ldimer

——— foldedL

Figure 4

Light Chain Constructions

PhoA

STII   Light Chain λ_{t0}

Promoter   Signal

TIR 1, 2, 3, 7, or 13

Heavy Chain Constructions

PhoA

STII   Heavy Chain λ_{t0}

Promoter   Signal

TIR 1, 2, 3, 7, or 13
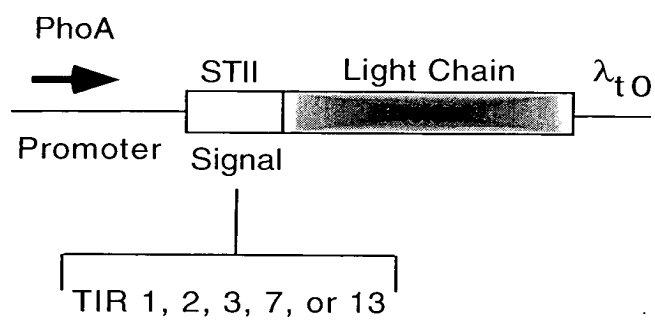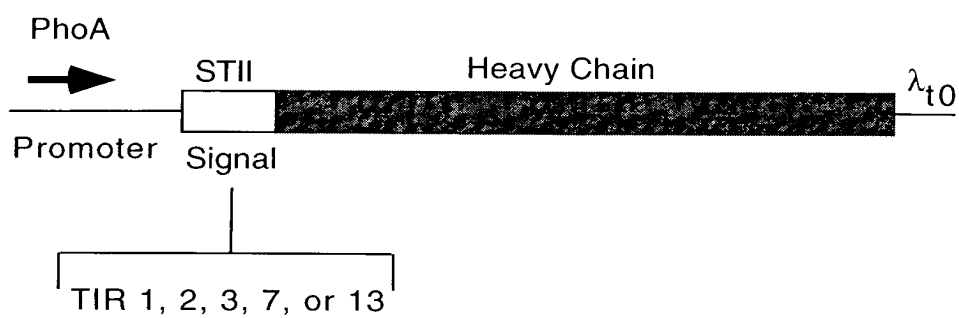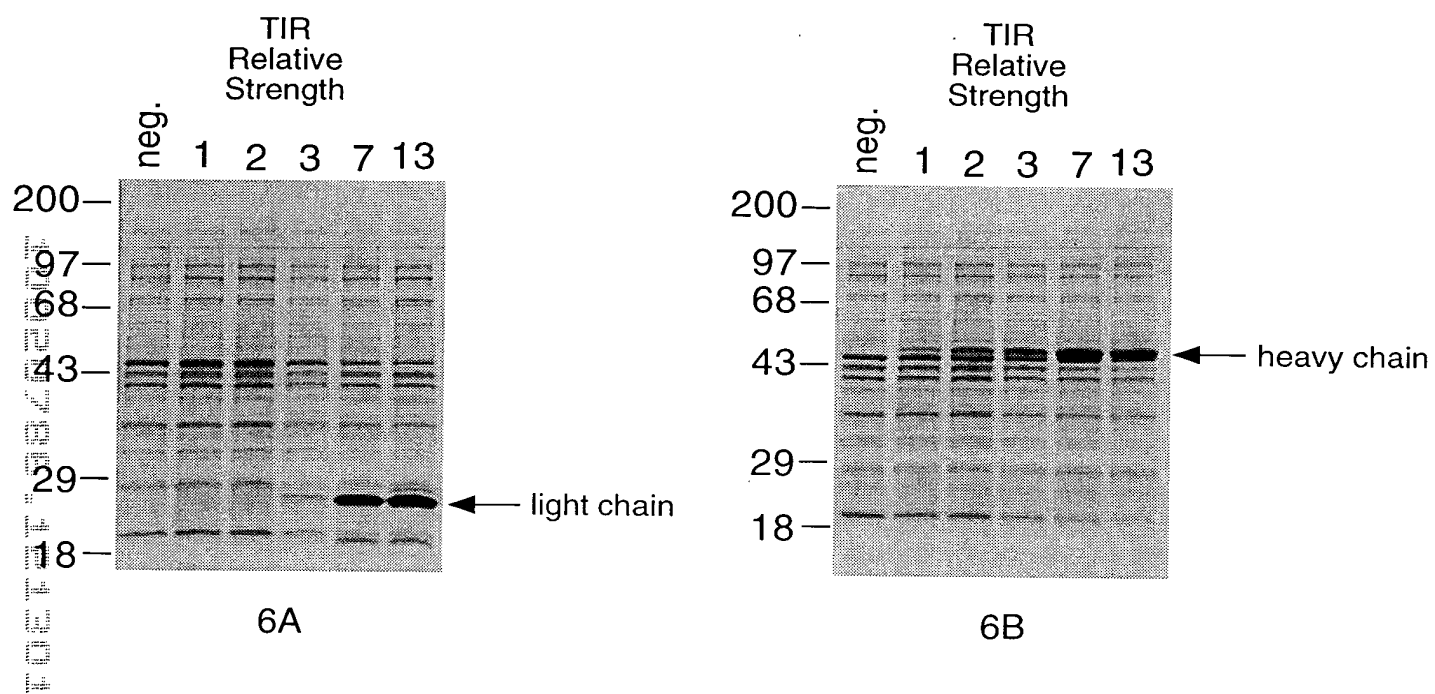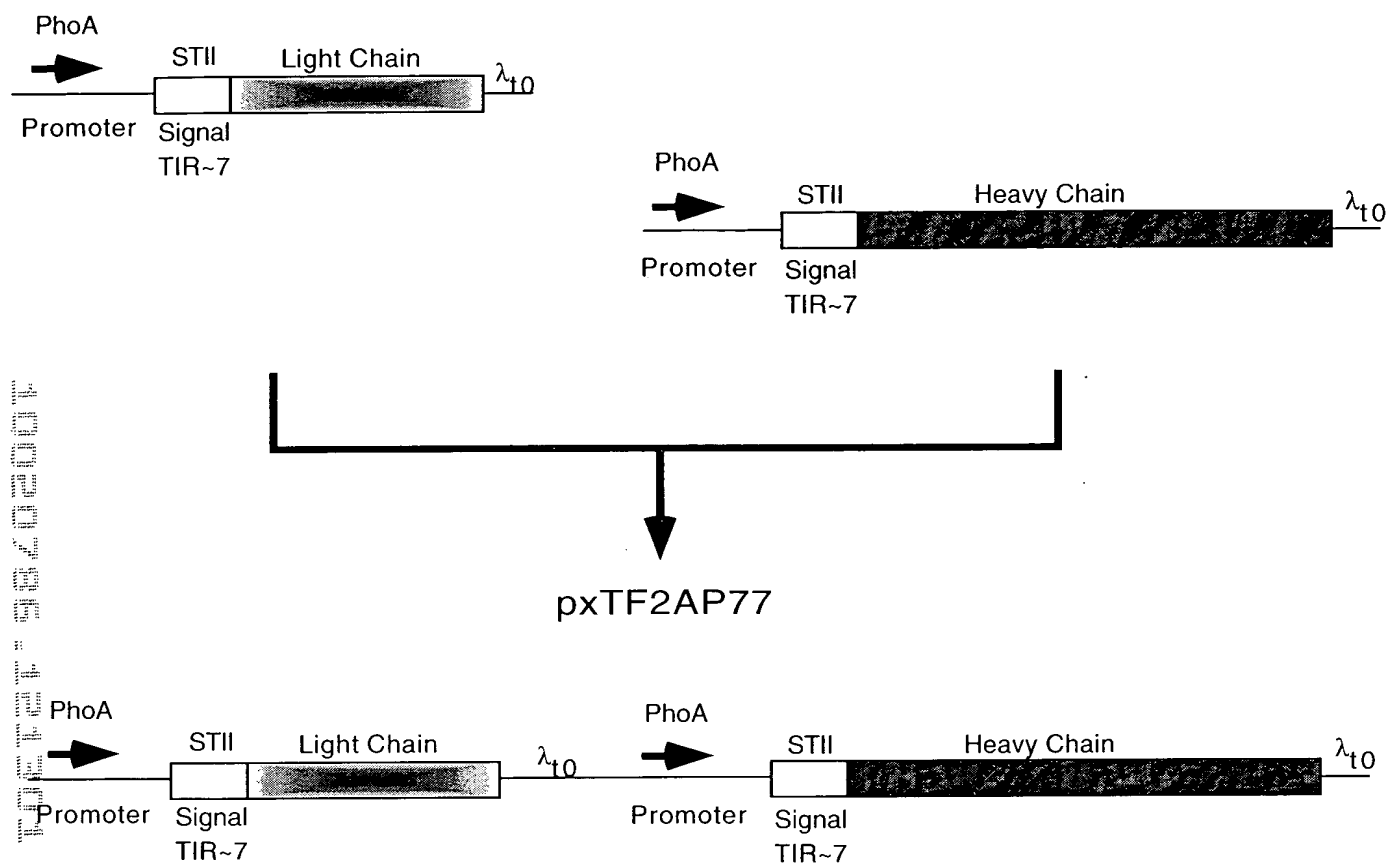
Figure 5

Figure 6

Figure 7
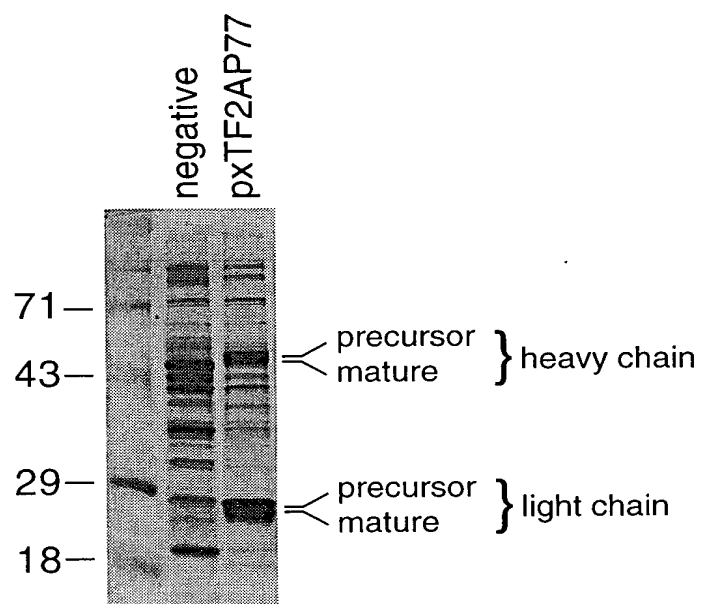
Figure 8

Separate Cistron Constructs

AP promoter · STII · light chain · λ to trans. term. · AP promoter · STII · heavy chain · λ to trans. term.

TIR · TIR

TIR (light)	TIR (heavy)	construct
1	1	paTF50
3	1	paTF70
1	3	paTF60
3	3	paTF80
7	3	paTF130
3	7	paTF140
7	7	pxTF2AP77

Figure 9

separate cistrons
reduced

neg.	1L 1H	3L 1H	1L 3H	3L 3H	7L 3H	3L 7H	7L 7H	

10A

—— heavy

—— light

separate cistrons
non-reduced

neg.	1L 1H	3L 1H	1L 3H	3L 3H	7L 3H	3L 7H	7L 7H	

10B

foldedH
Ldimer

—— foldedL
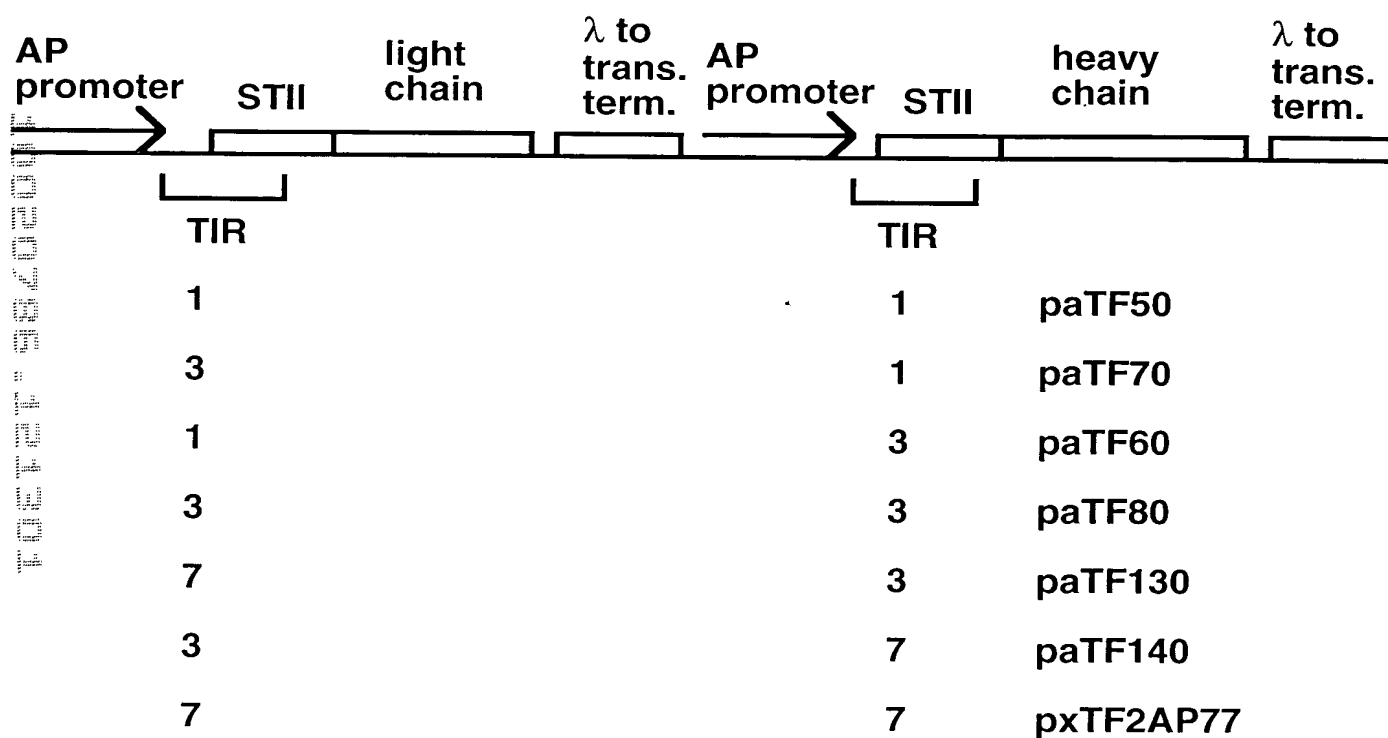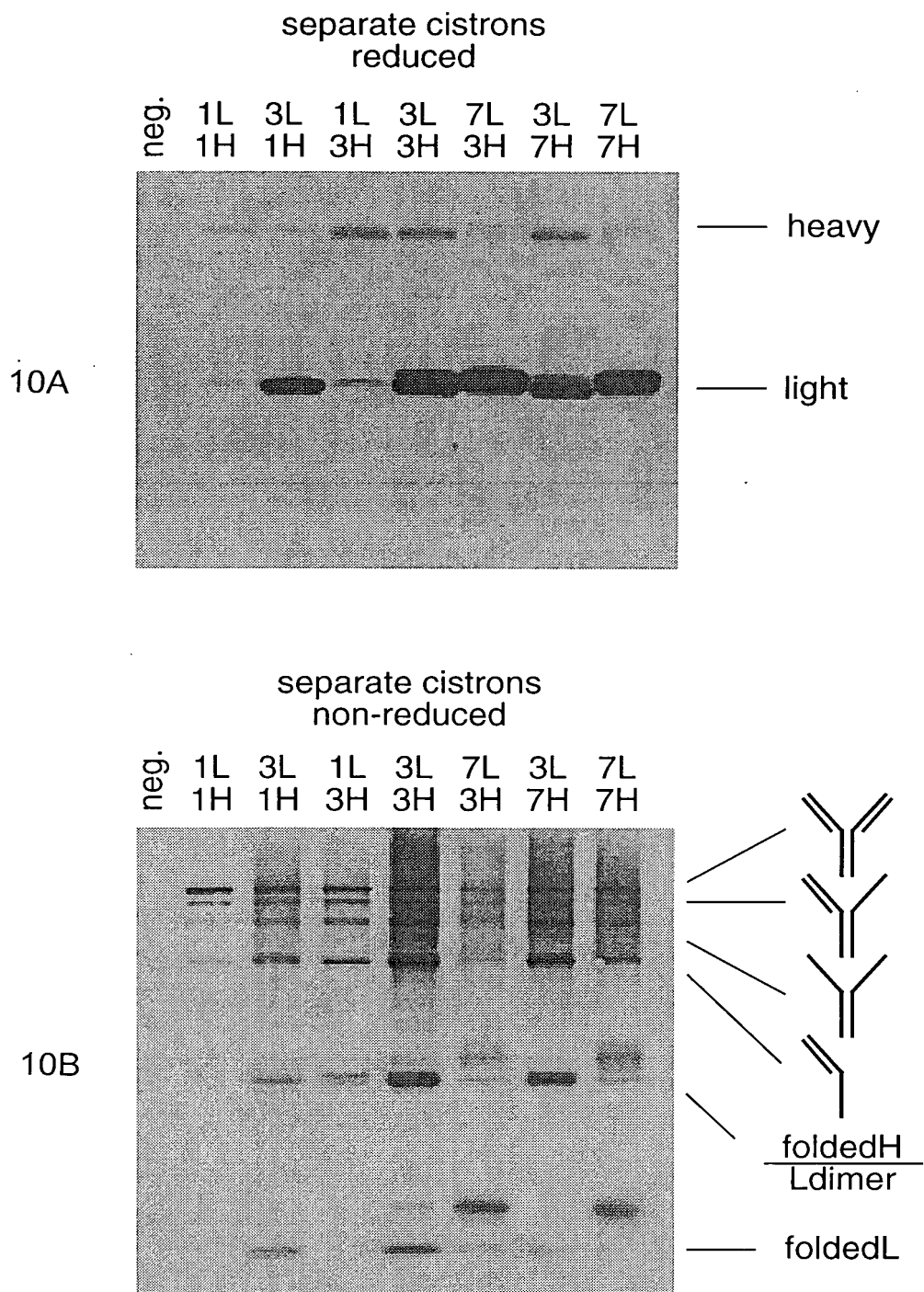
Figure 10
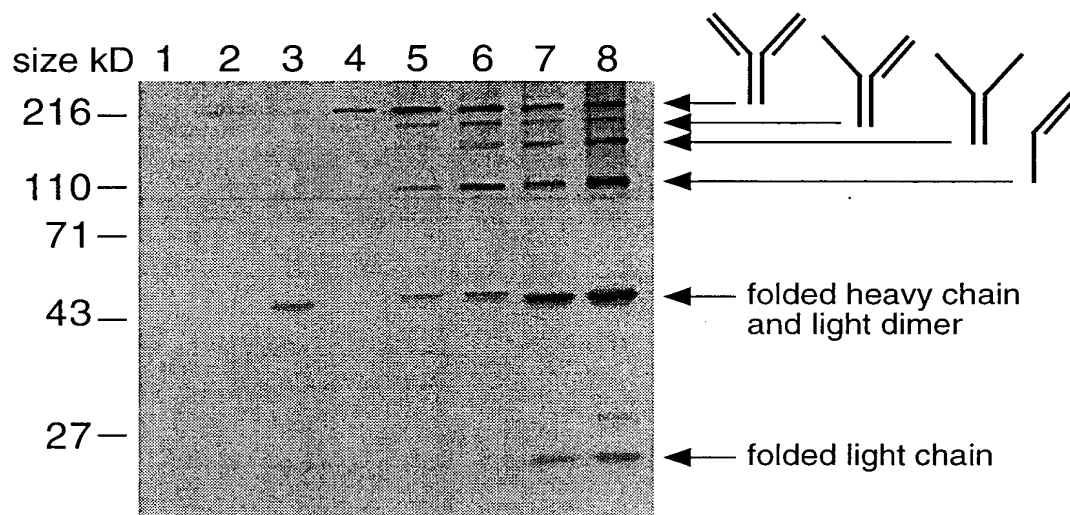
1) negative control
2) TIR 1-light, TIR 1-heavy, polycistronic
3) TIR 3-light, TIR 1-heavy, polycistronic
4) TIR 1-light, TIR 3-heavy, polycistronic
5) TIR 1-light, TIR 1-heavy, separate cistrons
6) TIR 1-light, TIR 3-heavy, separate cistrons
7) TIR 3-light, TIR 1-heavy, separate cistrons
8) TIR 3-light, TIR 3-heavy, separate cistrons

Figure 11
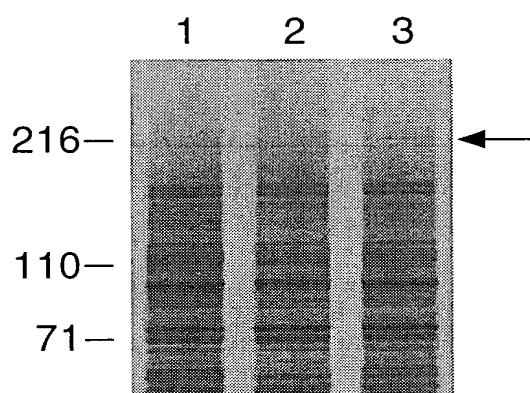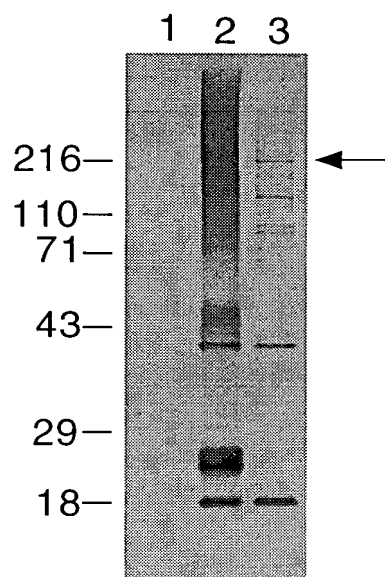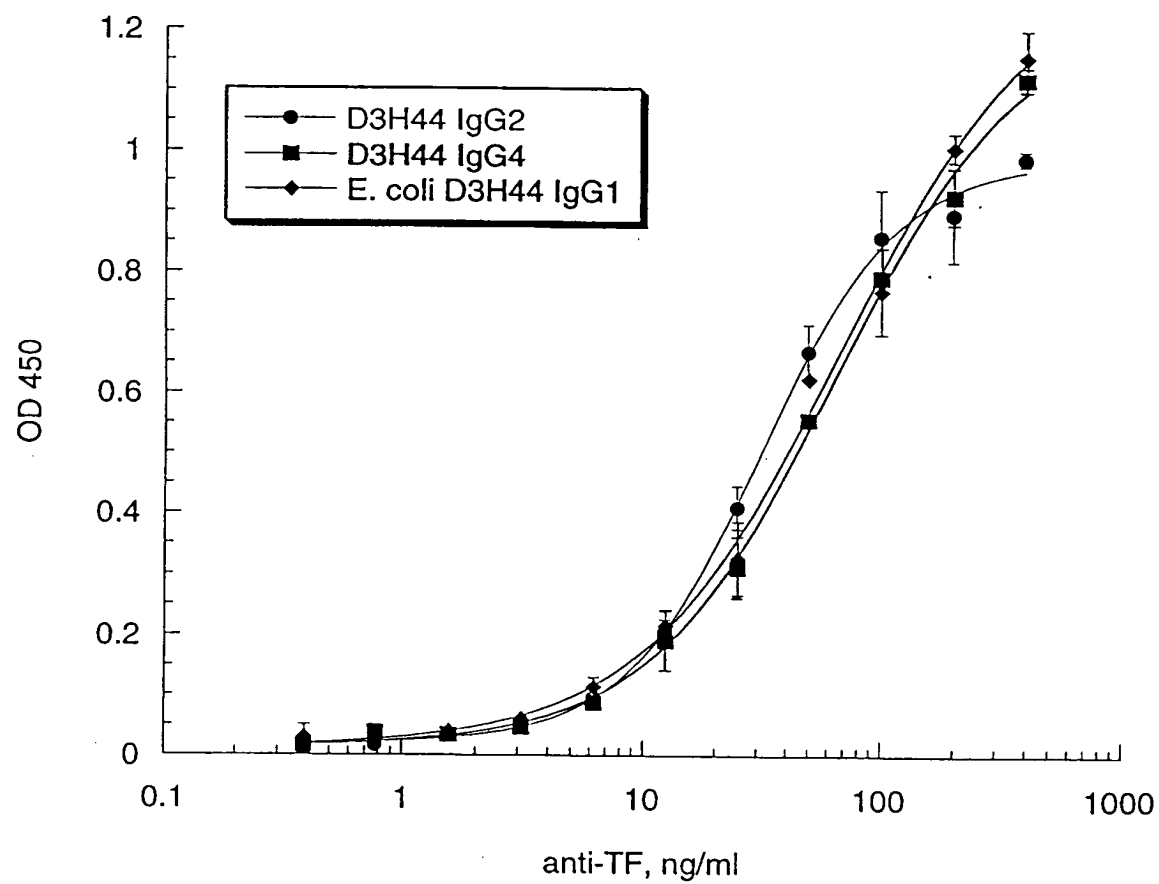
Figure 12

Figure 13
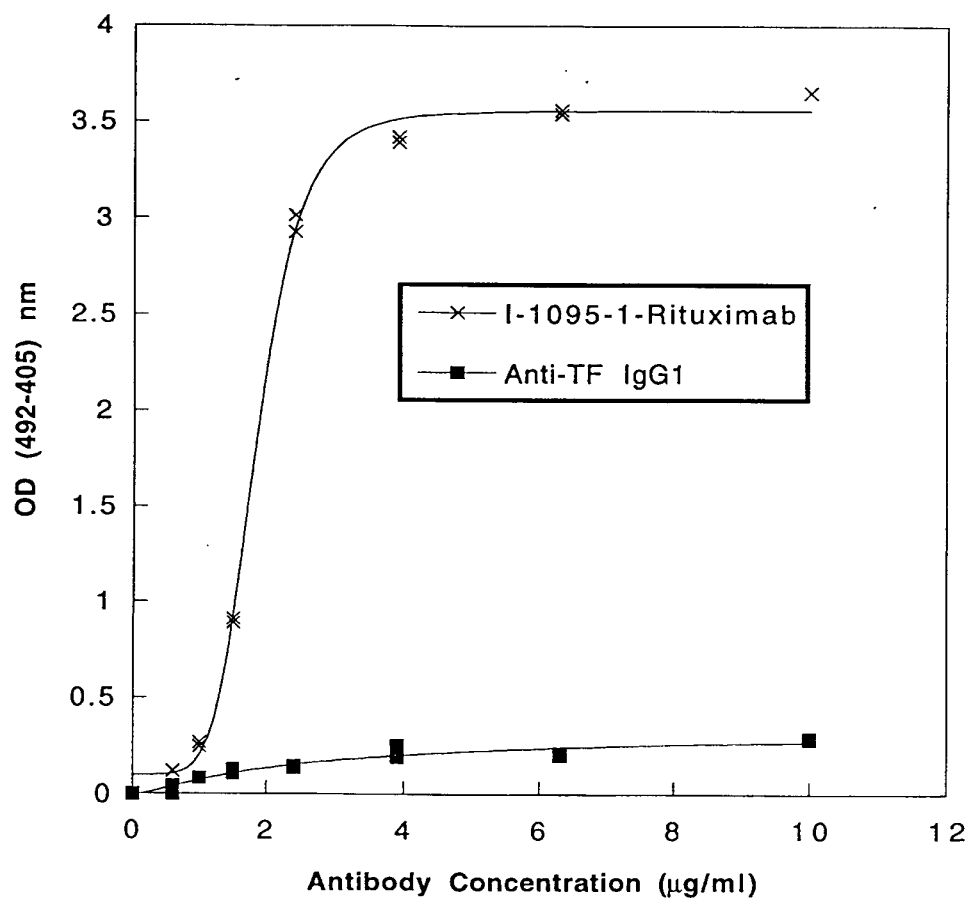
Figure 14
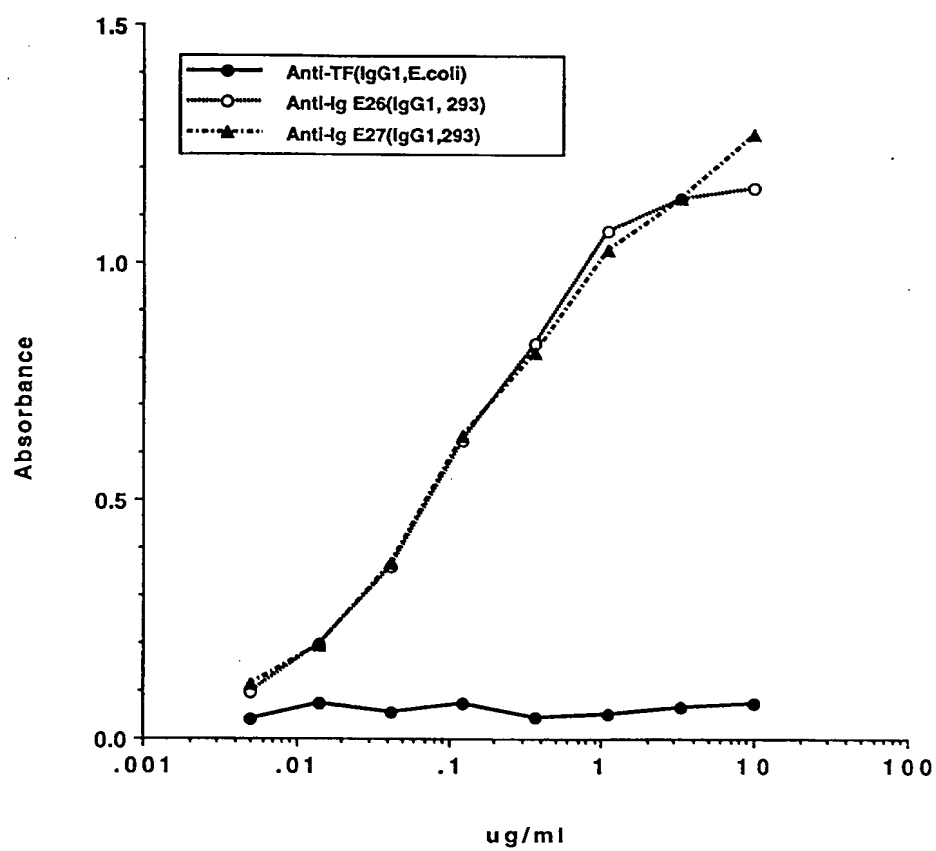
Figure 15
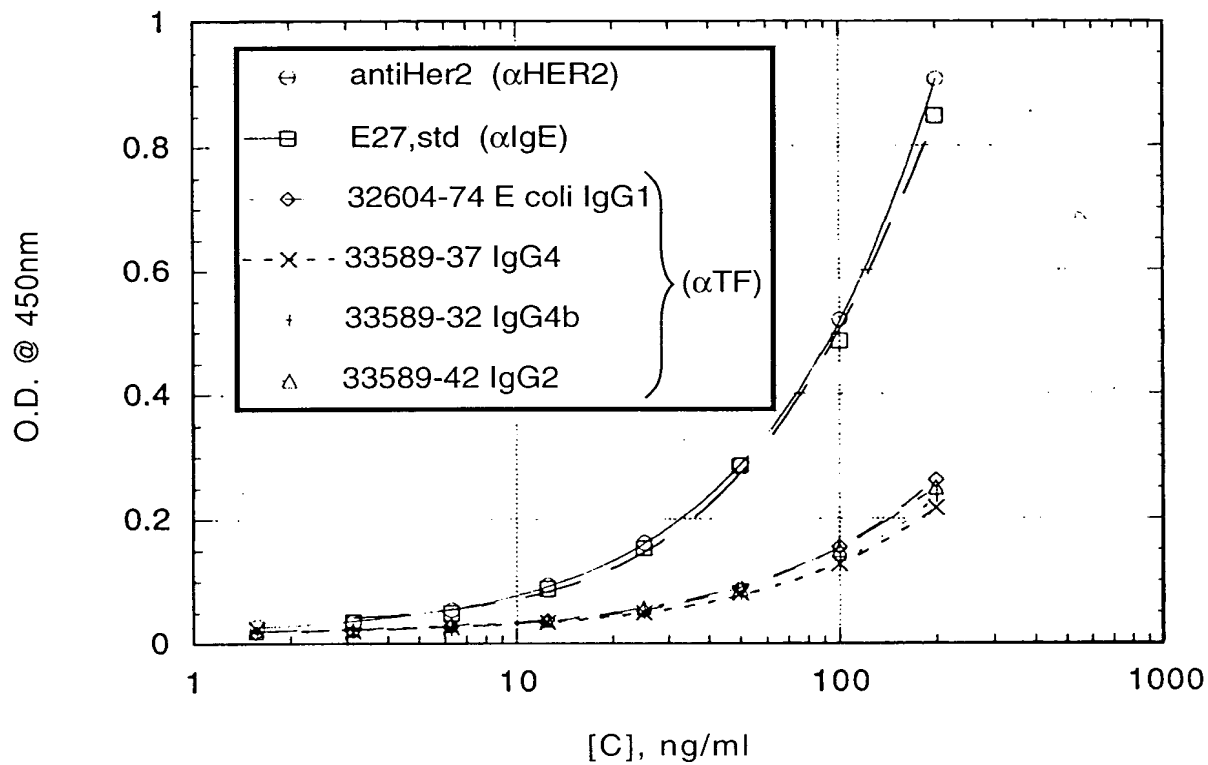
Figure 16

Figure 17

Figure 18

Figure 19

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   1  GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT
      CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA

 101  GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCCAACAGCG GTTGATTGAT CAGGTAGAGG
      CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGGTATAC CGGCGTTTAC CAACTAACTA GTCCATCTCC

 201  GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CAACGATACG GAGCTGCTGC GCGATTACGT TTGAAGCATC CTCGTCAGTA
      CCCGCGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GTTGCTATGC CTCGACGACG CGCTAATGCA AACTTCGTAG GAGCAGTCAT

 301  AAAAGTTAAT CTTTTCAACA GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTATT TTTTAATGTA GTACGCAAGT
      TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CGGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT CATGCGTTCA

 401  TCACGTAAAA AGGGTATCTA GAATTATGAA CTTCTTATAG CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTTTGGCCAT GCGTGATATC
      AGTGCATTTT TCCCATAGAT CTTAATACTT GAAGAATATC GCATTTCTTC TTGCATCTAT GTTCGTTTTT TCTATTGCTA CAAACGCGTA CGCACTATAG
   1                          M  K  N  I  A  F  L  L  A  S  M  F  V  F  S  I  A  T  N  A  Y  A  D  I
                              ^STII Signal Sequence TIR-1                 Anti-Tissue Factor Light Chain^

 501  CAGATGACCC AGTCCCCGAG CTCCCTGTCC GCGAGCGTCG GGGACCGCGT CACCATCACC TGCAGAGCCA GTGCGCGACAT CAAGAGCTAT CTGAACTGGT
      GTCTACTGGG TCAGGGGCTC GAGGGACAGG CGCTCGCAGC CCCTGGCGCA GTGGTAGTGG ACGTCTCGGT CACGCGCTGTA GTTCTCGATA GACTTGACCA
  26  Q  M  T  Q  S  P  S  S  L  S  A  S  V  G  D  R  V  T  I  T  C  R  A  S  Q  D  I  K  S  Y  L  N  W  Y

 601  ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA TTATGCTACT AGTCTCGCTG AAGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC
      TAGTTGTCTT TGGTCCTTTT CGAGGCTTTC ATGACTAAAT AATACGATGA TCAGAGCGAC TTCCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG
  60  Q  Q  K  P  G  K  A  P  K  V  L  I  Y  Y  A  T  S  L  A  E  G  V  P  S  R  F  S  G  S  G  S  G  T

 701  GGATTACACT CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTCT TCAGCACGGA GAGTCTCCAT GGACATTTGG ACAGGGTACC
      CCTAATGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGA AGTCGTGCCT CTCAGAGGTA CCTGTAAACC TGTCCCATGG
  93  D  Y  T  L  T  I  S  S  L  Q  P  E  D  F  A  T  Y  Y  C  L  Q  H  G  E  S  P  W  T  F  G  Q  G  T

 801  AAGGTGGAGA TCAAACGAAC TGTGGCTGCA CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT GTGTGCCTGC
      TTCCACCTCT AGTTTGCTTG ACACCGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG
 126  K  V  E  I  K  R  T  V  A  A  P  S  V  F  I  F  P  P  S  D  E  Q  L  K  S  G  T  A  S  V  V  C  L  L

 901  TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA
      ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT
 160  N  N  F  Y  P  R  E  A  K  V  Q  W  K  V  D  N  A  L  Q  S  G  N  S  Q  E  S  V  T  E  Q  D  S  K

1001  GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
      CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
 193  D  S  T  Y  S  L  S  S  T  L  T  L  S  K  A  D  Y  E  K  H  K  V  Y  A  C  E  V  T  H  Q  G  L  S

1101  TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT AGCCCGGACG CATCGTGGCG AGTCGGTAC  CGGGGATCT AGGCTTAACG
      AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TCGGGCCTGC GTAGCACCGC TCAGCCATG  GCCCCTAGA TCCGAATTGC
 226  S  P  V  T  K  S  F  N  R  G  E  C  O
```

Figure 20a

```
1201  CTCGGTTGCC GCCGGGCGT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
      GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCCATCT CGAAACCTCT AATAGCAGTG ACGTTACGAA

1301  CGCAAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGAGG GGGCGTAAAGC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
      GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401  AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAGTTAATC TTTTCAACAG GTTGTCACGG CCAGACTTA
      TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTGCC GGCTCTGAAT

1501  TAGTGCTTT GTTTTTATTT TTTAAATGTAT TTGTAACTAG TACGCAAGTT CACTCAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
      ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCCGTTCAA GTGCATTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAGAAGA
                                                                                        M  K  K  N  I  A  F  L  L
                                                                                        ^STII Signal Sequence TIR-1

1601  TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGGCTAC GCTGAGGTTC AGTCTGGTGA GTCTGGCCGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT
      ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCCGATG CGACTCCAAG TCAGACCACT CAGACCGGCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA
      A  S  M  F  V  F  S  I  A  T  N  A  Y  A  E  V  Q  L  V  E  S  G  G  G  L  V  Q  P  G  G  S  L  R

1701  TTGTCCTGTG CAGCTTCTGG AACAGAGACAC GTCGAAGACC GAAGTTATAA TTCCTCATGA TGTACGTGAC CCAGGCAGTC GCCCCGGGTA ATGGGTTGGA TTGATTGATC
      AACAGGACAC GTCGAAGACC GAAGTTATAA TTCCTCATGA TGTACGTGAC CCAGGCAGTC GCCCCGGGTA TCCCGGACCT TACCAACCT AACTAACTAG
      L  S  C  A  A  S  G  F  N  I  K  E  Y  Y  M  H  W  V  R  Q  A  P  G  K  G  L  E  W  V  G  L  I  D  P

1801  CAGAGCAAGG CAACACGATC TATGACCCGA AGTTCCAGGA CCGTGCCACT ATAAGCGCTG AAACAATTCCAA AACACCAGCA TACCTGCAGA TGAACAGCCT
      GTCTCGTTCC GTTGTGCTAG ATACTGGGCT TCAAGGTCCT TGGCACGGTGA TATTCGCGAC TGTTAAGGTT TTTGTGTCGT ATGGACGTCT ACTTGTCGGA
      E  Q  G  N  T  I  Y  D  P  K  F  Q  D  R  A  T  I  S  A  D  N  S  K  N  T  A  Y  L  Q  M  N  S  L

1901  GCGTGCTGAG GACACTGCCG TCTATTATTG TGCTCGAGAC ACGGCGCTT ACTTCGACTA CTGGGGTCAA CTGGGGCTAG GGAACCCTGG CTCACCGTCTC CTCGGCCTCC
      CGCACGACTC CTGTGACGGC AGATAATAAC ACGAGCTCTG TGCCGCGGAA TGAAGCTGAT GACCCCAGTT CCTTGGGACC GAGTGGCAGAG GAGCCGGAGG
      R  A  E  D  T  A  V  Y  Y  C  A  R  D  T  A  A  Y  F  D  Y  W  G  Q  G  T  L  V  T  V  S  A  S

2001  ACCAAGGGCC CATCGGTCTT CCCCCTGGCA GGGGGACCGT GGGGGACCGT AGAGCACCTC TGGGGGCACA GCGCCCCTGG GCTGCCTGGT CAAGGACTAC TTCCCCGAAC
      TGGTTCCCGG GTAGCCAGAA GGGGGACCGT CCCCCTGGCA TCTCGTGGAG ACCCCGTGT CGCCGGGACC CGACGGACCA GTTCCTGATG AAGGGGCTTG
      T  K  G  P  S  V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L  G  C  L  V  K  D  Y  F  P  E  P

2101  CGGTGACGGT GTCGTGGAAC TCAGGCGCCC TGACCAGCGG CGTGCACACC TTCCCGGCTG CGTGCACAGTC TCCTACAGTC CTACTCCCTCA GCAGCGTGGT
      GCCACTGCCA CAGCACCTTG AGTCCGCGGG ACTGGTCGCC GCACGTGTGG AAGGCCCGAC AGGATGTCAG AGGTGTCGAG ATGAGGGAGT CGTCGCACCA
      V  T  V  S  W  N  S  G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G  L  Y  S  L  S  S  V  V

2201  GACTGTGCCC TCTAGCAGCT TGGGCACCCA GACCTACACC TGCAACGTGA ATCACAAGCC CAGCAACACC AAGGTGGACA AGAAAGTTGA GCCCAAATCT
      CTGACACGGG AGATCGTCGA ACCCGTGGGT CTGGATGTGG ACGTTGCACT TAGTGTTCGG GTCGTTGTGG TTCCACCTGT TCTTTCAACT CGGGTTTAGA
      T  V  P  S  S  S  L  G  T  Q  T  Y  I  C  N  V  N  H  K  P  S  N  T  K  V  D  K  K  V  E  P  K  S

2301  TGTGACAAAA CTCACACATG CCCACCGTGC CCAGCACCTG AACTCCTGGG GGGACCGTCA GTCTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA
      ACACTGTTTT GAGTGTGTAC GGGTGGCACG GGTCGTGGAC TTGAGGACCC CCCTGGCAGT CAGAAGGAGA AGGGGGGTTT TGGGTTCCTG TGGGAGTACT
      C  D  K  T  H  T  C  P  P  C  P  A  P  E  L  L  G  G  P  S  V  F  L  F  P  P  K  P  K  D  T  L  M  I

2401  TCTCCCGGAC CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA GACCCTGAGG TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA
      AGAGGGCCTG GGGACTCCAG TGTACGCACC ACCACCTGCA CTCGGTGCTT CTGGGACTCC AGTTCAAGTT GACCATGCAC CTGCCGCACC TCCACGTATT
      S  R  T  P  E  V  T  C  V  V  V  D  V  S  H  E  D  P  E  V  K  F  N  W  Y  V  D  G  V  E  V  H  N
```

Figure 20b

```
2501 TGCCAAGACA AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG TCAGCGTCCT CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC
     ACGGTTCTGT TTCGGCGCCC TCCTCGTCAT GTTGTCGTGC ATGGCACACC AGTCGCAGGA GTGGCAGGAC GTGGTCCTGA CCGACTTACC GTTCCTCATG
310  A  K  T   K  P  R  E   E  Q  Y    N  S  T    Y  R  V  V   S  V  L    T  V  L    H  Q  D  W   L  N  G    K  E  Y

2601 AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC
     TTCACGTTCC AGAGGTTGTT TCGGGAGGGT CGGGGGTAGC TCTTTTGGTA GAGGTTTCGG TTTCCCGTCG GGGCTCTTGG TGTCCACATG TGGGACGGGG
343  K  C  K   V  S  N  K   A  L  P    A  P  I    E  K  T  I   S  K  A    K  G  Q   P  R  E  P   Q  V  Y    T  L  P  P

2701 CATCCCGGGA AGAGATGACC AAGAACCAGG TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA
     GTAGGGCCCT TCTCTACTGG TTCTTGGTCC AGTCGGACTG GACGGACCAG TTTCCGAAGA TAGGGTCGCT GTAGCGGCAC CTCACCCTCT CGTTACCCGT
377  S  R  E   E  M  T    K  N  Q  V   S  L  T    C  L  V    K  G  F  Y   P  S  D    I  A  V    E  W  E  S   N  G  Q

2801 GCCGGAGAAC AACTACAAGA CCACGCCTCC CGTGCTGGAC TCCGACGGCT CCTTCTTCCT CTACAGCAAG CTCACCGTGG ACAAGAGCAG GTGGCAGCAG
     CGGCCTCTTG TTGATGTTCT GGTGCGGAGG GCACGACCTG AGGCTGCCGA GGAAGAAGGA GATGTCGTTC GAGTGGCACC TGTTCTCGTC CACCGTCGTC
410  P  E  N   N  Y  K  T   T  P  P    V  L  D    S  D  G  S   F  F  L    Y  S  K    L  T  V  D   K  S  R    W  Q  Q

2901 GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATAAGCA TGCCGACGGCC
     CCCTTGCAGA AGAGTACGAG GCACTACGTA CTCCGAGACG GTGTTGGTGAT GTGCGTCTTC TCGGAGAGGG ACAGAGGCCC ATTTATTCGT ACGCTGCCGG
443  G  N  V   F  S  C  S   V  M  H    E  A  L    H  N  H  Y   T  Q  K    S  L  S    L  S  P  G   K  O

3001 CTAGAGTCCC TAACGCTCGG TTGCCGCCGG GCGTTTTTTA TTGTTAACTC ATGTTTGACA GCTTATCATC GATAAGCTTT AATGCGGTAG TTTATCACAG
     GATCTCAGGG ATTGCGAGCC AACGGCGGCC CGCAAAAAAT AACAATTGAG TACAAACTGT CGAATAGTAG CTATTCGAAA TTACGCCATC AAATAGTGTC

3101 TTAAATTGCT AACGCAGTCA GGCACCGTGT ATGAAATCTA ACAATGCGCT CATCGTCATC CTCGGCACCG TCACCCTGGA TGCTGTAGGC ATAGGCTTGG
     AATTTAACGA TTGCGTCAGT CCGTGGCACA TACTTTAGAT TGTTACGCGA GTAGCAGTAG GAGCCGTGGC AGTGGGACCT ACGACATCCG TATCCGAACC
                                                ^Start Tet Resistance Coding Sequence

3201 TTATGCCGGT ACTGCCGGGC CTCTTGCGGG TATATCGTCCA TTCCGACAGC ATCGCCAGTC ATCATGGCGT ACTATGGCGT GCTGCTAGCG CTATATGCGT TGATGCAATT
     AATACGGCCA TGACGGCCCG GAGAACGCCC TATAGCAGGT AAGGCTGTCG TAGCGGTCAG TGATACCGCA CGACGATCGC GATATACGCA ACTACGTTAA

3301
```

Figure 20c

```
  1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAGA AGAGTCGAAT
    CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA

101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG
    CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGTTATAC CGCGTTTTAC TGGTTGTCGC CAACTAACTA GTCCATCTCC

201 GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CGACGATACG GAGCTGTCGC GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
    CCCGCGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT

301 AAAAGTTAAT CTTTTCACCA GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTATT TTTTAATGTA TTTGTAACTA GTACGCAAGT
    TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CGGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AAACATTGAT CATGCGGTTCA

401 TCACGTAAAA AGGGTATCTA GAATTATGAA GAAGAATATC TTGCATCTAT GTTCGTTTTT TCTATTGCTA CAAACGCGTA CCCTGATATC
    AGTGCATTTT TCCCATAGAT CTTAAGTACT CTTCTTATAG CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTTTGCGCAT GCGACTATAG
                                       M  K  N  I   A  F  L  L    A  S  M   F  V  F    S  I  A  T   N  A  Y    A  D  I
  1                                    ^STII Signal TIR -1                                  Anti-VEGF Light chain^

501 CAGTTGACCC AGTCCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCAGCGCAA GTCAGGATAT TAGCAACTAT TTAAACTGGT
    GTCAACTGGG TCAGGGGCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGTCGCGTT CAGTCCGCGTT ATATCGTTGATA AATTTGACCA
 26 Q  L  T  Q  S  P  S  S  L  S   A  S  V  G   D  R  V   T  I  T    C  S  A  S   Q  D  I   S  N  Y    L  N  W  Y

601 ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA CTTCACCTCC TCTCTCCACT CTTCGCTTC TCTGGATCGG GTTCTGGGAC
    TAGTTGTCTT TGGTCCTTTT CGAGGCTTTC ATGACTAAAT GAAGTGGAGG AGAGAGGTGA GAAGCGAAG AGACCTAGGC CAAGACCCTG
 60 Q  Q  K   P  G  K   A  P  K  V   L  I  Y    F  T  S    S  L  H  S   G  V  P    S  R  F    S  G  S  G   S  G  T

701 GGATTTCACT CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTCA ACAGTATAGC ACCGTGCCGT GGACGTTTGG ACAGGGTACC
    CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGT TGTCATATCG TGGCACGGCA CCTGCAAACC TGTCCCATGG
 93 D  F  T   L  T  I  S   S  L  Q    P  E  D   F  A  T  Y   Y  C  Q    Q  Y  S    T  V  P  W   T  F  G    Q  G  T

801 AAGGTGGAGA TCAAACGAAC TGTGGCTGCA CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT GTGTGCCTGC
    TTCCACCTCT AGTTTGCTTG ACACCGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG
126 K  V  E   I  K  R  T   V  A  A    P  S  V   F  I  F  P   P  S  D    E  Q  L  K   S  G  T    A  S  V  V   C  L  L

901 TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA
    ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT
160 N  N  F   Y  P  R   E  A  K  V   Q  W  K    V  D  N   A  L  Q  S   G  N  S    Q  E  S    V  T  E  Q   D  S  K

1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
     CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
193 D  S  T   Y  S  L  S   S  T  L    T  L  S   K  A  D  Y   E  K  H    K  V  Y    A  C  E  V   T  H  Q    G  L  S

1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGTCGGTTAC CCGGGGATCT AGGCCTAACG
     AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCAGCCAATG GGCCCCTAGA TCCGGATTGC
226 S  P  V  T   K  S  F    N  R  G   E  C  O
```

Figure 2la

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1201  CTCGGTTGCC GCCGGGCGGT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
      GAGCCAACGG CGGCCCGCCA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA

1301  CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGGCCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
      GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCCGGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401  AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
      TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT

1501  TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CAGTAAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
      ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTCATTTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
                                                                         M  K  K  N  I  A   F  L  L
                                                                                        ^STII Signal TIR-1
        1

1601  TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGGTAC GCTGAGGTTC AGCTGGTGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT
      ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGGCCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA
       10  A  S  M   F  V  F  S   I  A  T   N  A  Y   A  E  V  Q  L  V  E   S  G  G   G  L  V  Q   P  G  G   S  L  R
                                                                   ^Anti-VEGF Heavy Chain

1701  TTGTCCTGTG CAGCTTCTGG CTACGACTTC ACGCACTACG GTATGAACTG GGTCCGTCAG AGGCCCGGTA AAGGGTTGGA ATGGGTTGGA TGGATTAACA
      AACAGGACAC GTCGAAGACC GATGCTGAAG TGCGTGATGC CATACTTGAC CCAGGCAGTC TCCGGGCCAT TTCCCAACCT TACCCAACCT ACCTAATTGT
       43  L  S  C  A   A  S  G   Y  D  F   T  H  Y  G   M  N  W   V  R  Q   A  P  G  K   G  L  E   W  V  G   W  I  N  T

1801  CCTATACCGG TGAACCGACC TATGTGCGG ATTTCAAACG TCGTTCACT TTTTCTTTAG ACACATCCAA AAGCACAGCA TACCTGCAGA TGAACAGCCT
      GGATATGGCC ACTTGGCTGG ATACAGCGCC TAAAGTTTGC AGCAAGTGA AAAAGAAATC TGTGTAGGTT TTCGTGTCGT ATGGACGTCT ACTTGTCGGA
       77  Y  T  G   E  P  T   Y  V  A  A  D   F  K  R   R  F  T   F  S  L  D   T  S  K   S  T  A   Y  L  Q  M   N  S  L

1901  GCGCGCTGAG GACACTGCCG TCTATTACTG TGCAAAGTAC CCGTACTATT ACGGCACGAG CCACTGGTAT TTCGACGTCT GGGGTCAAGG AACCCTGGTC
      CGCGCGACTC CTGTGACGGC AGATAATGAC ACGTTTCATG GGCATGATAA TGCCGTGCTC GGTGACCATA AAGCTGCAGA CCCCAGTTCC TTGGGACCAG
      110  R  A  E   D  T  A  V   V  Y  Y  C   A  K  Y   P  Y  Y  Y   Y  G  T  S   H  W  Y   F  D  V  W   G  Q  G   T  L  V

2001  ACCGTCTCCT CGGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA
      TGGCAGAGGA GCCGGAGGTG GTTCCCGGGT AGCCAGAAGG GGGACCGTGG GAGGAGGTTC TCGTGGAGAC CCCGTGTCG CCGGGACCCG ACGGACCAGT
      143  T  V  S  S   A  S  T   K  G  P   S  V  F  P   L  A  P   S  S  K   S  T  S  G   G  T  A   A  L  G   C  L  V  K

2101  AGGACTACTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA
      TCCTGATGAA GGGGCTTGGC CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA GGGCCGACAG GATGTCAGGA GTCCTGAGAT
      177  D  Y  F   P  E  P   V  T  V  S   W  N  S   G  A  L   T  S  G  V   H  T  F   P  A  V   L  Q  S  S   G  L  Y

2201  CTCCCTCAGC AGCGTGGTGA CTGTGCCCTC TAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG
      GAGGGAGTCG TCGCACCACT GACACGGGAG ATCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA GTGTTCGGGT CGTTGTGGTT CCACCTGTTC
      210  S  L  S   S  V  V  T   V  P  S   S  S  L   G  T  Q  T   Y  I  C   N  V  N   H  K  P  S   N  T  K   V  D  K

2301  AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCTCTTTC CCCCCAAAAC
      TTTCAACTCG GGTTTAGAAC ACTGTTTTGA GTGTGTACGG GTGGCACGGG TCGTGGACTT GAGGACCCCC CTGGCAGTCA GAAGAGAAAG GGGGGTTTTG
      243  K  V  E  P   S  C  D   K  T   H  T  C  P   P  C  P   A  P  E   L  L  G  G   P  S  V   F  L  F   P  P  K  P

2401  CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA
      GGTTCCTGTG GGAGTACTAG AGGGCCTGGG GACTCCAGTG TACGCACCAC CACCTGCACT CGGTGCTTCT GGGACTCCAG TTCAAGTTGA CCATGCACCT
      277  K  D  T   L  M  I   S  R  T  P   E  V  T   C  V  V   V  D  V  S   H  E  D   P  E  V   K  F  N  W   Y  V  D
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Figure 21b

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2501 CGGGCTGGAG GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG
     GCCGCACCTC CACGTATTAC GGTTCTGTTT CGGGCGCCCTC CTCGTCATGT TGTCGTGCAT GGCACACCAG TCGCAGGAGT GGTCCTGACC
310  G  V  E    V  H  N  A    K  T  K    P  R  E    E  Q  Y  N    S  T  Y    R  V  V    S  V  L  T    V  L  H    Q  D  W

2601 CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
     GACTTACCGT TCCTCATGTT CACGTTCCAG AGGTTGTTTC GGGAGGGTCG TTTTGGTAGA GGTTTCGGTT TCCCGTCGGG GCTCTTGGTG
343  L  N  G  K    E  Y  K    C  K  V    S  N  K  A    L  P  A    P  I  E    K  T  I  S    K  A  K    G  Q  P    R  E  P  Q

2701 AGGTGTACAC CCTGCCCCCA TCCCGGGAAG AGATGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
     TCCACATGTG GGACGGGGGT AGGGCCCTTC TCTACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT TCCGAAGATA GGGTCGCTGT AGCGGCACCT
377  V  Y  T    L  P  P    S  R  E  E    M  T  K    N  Q  V    S  L  T  C    L  V  K    G  F  Y    P  S  D  I    A  V  E

2801 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC
     CACCCTCTCG TTACCCGTCG GCCTCTTGTT GATGTTCTGG TGCGGAGGGC ACGACCTGAG AAGAAGGAGA TGTCGTTCGA GTGGCACCTG
410  W  E  S    N  G  Q  P    E  N  N    Y  K  T    T  P  P  V    L  D  S    D  G  S    F  F  L  Y    S  K  L    T  V  D

2901 AAGAGCAGGT GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
     TTCTCGTCCA CCGTCGTCCC CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG TTGGTGATGT GCGTCTTCTC GGAGAGGGAC AGAGGCCCAT
443  K  S  R  W    Q  Q  G    N  V  F    S  C  S  V    M  H  E    A  L  H    N  H  Y  T    Q  K  S    L  S  L    S  P  G  K

3001 AATAAGCATG CGACGGCCCT AGAGTCCCTA ACGGTCGGGT GCCGCCGGGC GTTTTTATT GTTAACTCAT GTTTGACAGC TTATCATGA TTAAGCTTAA
     TTATTCGTAC GCTGCCGGGA TCTCAGGGAT TGCCAGCCCA CGGCGGCCCG CAAAAAATAA CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAATT
477  O

3101 TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG
     ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC
                                                              ^Start Tet Resistance Coding Sequence

3201 CTGTAGGCAT AGGCTTGGTT ATGCGGGGAT TGCCGGGGCCT CTTGCGGGCT ATCGTCCATT CCGACAGCAT CGCCAGCGAC TATGGCGTGC TGCTAGCGCT
     GACATCCGTA TCCGAACCAA TACGGCCATG TACGGCCCTA AGAACGCCCGA GAACGCCCGA TAGCAGTAA GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA

3301
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Figure 21c

Figure 22